TECHNICAL SUMMARY OF RESULTS

[2006-002695-17; Debio-025-HCV-203]

Name of sponsor: Debiopharm International S.A.	**Individual study table referring to module 5 of the dossier**	**(For national authority use only)**
Name of finished product: NA	**Volume:**	
Name of active ingredient: DEBIO-025	**Page:**	

Title of study:	A multi-centre, randomised, double-blind, placebo-controlled escalating dose-ranging phase II study on the efficacy of DEBIO-025 to reduce HCV viral load in combination with PEGASYS® (180 µg/week) in treatment naïve patients with chronic hepatitis C and on the safety of this combination therapy [2006-002695-17; Debio-025-HCV-203]	
Principal Investigator:	Robert Flisiak, MD, PhD	
Study centres:	10 clinical centres: 5 in Poland, 3 in Canada, and 2 in Italy.	
Publication (reference):	None.	
Study period:	From 27-Sep-2006 to 23-Aug-2007	**Phase of development:** Phase II

Objectives:

Primary:

To determine the minimum effective dose (MED) of DEBIO-025 in a 4-week treatment course of daily oral DEBIO-025 combined with once weekly 180 µg PEGASYS® (pegylated interferon alfa-2a) injections in chronically hepatitis C virus (HCV) infected treatment-naïve patients that shows an additive anti-HCV effect when compared to PEGASYS® 180 µg weekly monotherapy.

Secondary:

- To demonstrate that an effective and well tolerated dose of oral DEBIO-025 combined with 180 µg weekly PEGASYS® has an additive effect on HCV viral load reduction compared to the same dose of DEBIO-025 monotherapy;
- to evaluate the safety of the daily oral DEBIO-025 and weekly injected 180 µg PEGASYS® combination therapy;
- to establish in a subset of patients (at least 6 patients per treatment group, minimum total 30 patients) the pharmacokinetic (PK) profile of DEBIO-025 and PEGASYS® as single agents and in combination to explore potential drug-drug interactions.

Methodology:

International, multi-centre, randomised, double-blind, placebo-controlled, escalating multiple dose, add-on therapy of DEBIO-025.

The study was divided into 3 periods:

- Period 1 (screening): after patient had received appropriate information from the investigator and had given written consent, all screening procedures were applied;
- Period 2 (treatment): patients who fulfilled all inclusion & exclusion criteria were included in the study and at weekly intervals HCV viral load, adverse events (AEs), and laboratory safety parameters were assessed. A PK profile of DEBIO-025 (trough level) was established using concentrations on days 1, 8, 15, 22, 29, and 50. A 12-hour PK profile of DEBIO-025

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and PEGASYS® was established on days 1 and 29 in a subset of study patients (n = 6/treatment group);

Period 3 (follow-up): a follow-up visit was planned on day 50 after a 3-week washout period and the investigator discussed treatment options with the patient.

Number of patients:

90 planned (3 cohorts of 24 patients [cohorts I to III] and 1 cohort of 18 patients [cohort IV]), 90 randomised, 90 treated, 86 completed, and 4 discontinued due to an AE.

Diagnosis and main criteria for inclusion:

HCV positive male or female patients aged 18 – 70 years inclusive with a body mass index (BMI) between 18 and 29 kg/m^2 inclusive and naïve to anti-HCV treatments.

Test product, dose and mode of administration:

- **Cohort I**: administration of 200 mg DEBIO-025 b.i.d. from day 1 to day 7 and 200 mg DEBIO-025 o.d. from day 8 to day 29. Furthermore these patients were administered 180 µg PEGASYS® once a week;
- **Cohort II**: administration of 600 mg DEBIO-025 b.i.d. from day 1 to day 7 and 600 mg DEBIO-025 o.d. from day 8 to day 29. Furthermore these patients were administered 180 µg PEGASYS® once a week;
- **Cohort III**: administration of 1000 mg DEBIO-025 b.i.d. from day 1 to day 7 and 1000 mg DEBIO-025 o.d. from day 8 to day 29. Furthermore these patients were administered 180 µg PEGASYS® once a week;
- **Cohort IV**: administration of 1000 mg DEBIO-025 b.i.d. from day 1 to 7 and 1000 mg DEBIO-025 o.d. from day 8 to day 29.

Duration of treatment:

The maximum study duration for each patient was 11 weeks (a screening period and a treatment period of 4 weeks each, followed by a follow-up of 3 weeks).

Reference product, dose and mode of administration, batch number:

Cohorts I, II, and III: DEBIO-025 placebo from day 1 to day 29. Injection of PEGASYS® (180 µg) once a week.

Criteria for evaluation:

Efficacy:

- Primary endpoint: maximum $\log_{10}$ viral load reduction (HCV RNA IU/mL) from pre- treatment (day 1) to any on-treatment (day 2 to day 29) or post-treatment (day 30 to day 50) value;
- Secondary endpoints: proportion of patients with a viral load reduction of at least 2 $\log_{10}$ after 4 weeks of treatment (day 29). Proportion of patients with an undetectable viral load after 4 weeks of treatment (day 29).

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Safety:

Incidence of AEs, change in vital signs, haematology, coagulation, biochemistry, urinalysis, 12-lead electrocardiogram (ECG) parameters (RR, PR, QRS, QT, and QTcB intervals).

Pharmacokinetics:

Plasma concentrations of DEBIO-025 and PEGASYS® (samples: from day 1 pre-treatment up to day 50) and, if applicable, the following PK calculations:

- DEBIO-025: C_{max}, t_{max}, and $AUC_{0\text{-}12h}$ at day 1; C_{0h} at days 1, 8, 15, 22, 29; C_{min}, C_{max}, $C_{ss\ av}$, t_{max}, $AUC_{0\text{-}12h}$, $AUC_{0\text{-}24h}$, fluctuation index ($Flux_i$), accumulation ratios (AR), and Cl/F at day 29; C_{504h} at day 50;
- PEGASYS®: C_{max}, t_{max}, and $AUC_{0\text{-}12h}$ at day 1; C_{0h} at days 1, 8, 15, 22, 29; C_{max}, t_{max}, $AUC_{0\text{-}12h}$, $AUC_{0\text{-}24h}$, and AR at day 29; C_{504h} at day 50.

Statistical methods:

Interim analysis:

Analyses by an independent data monitoring committee (DMC) of safety and PK/efficacy modelling took place to provide recommendation about DEBIO-025 dose for each subsequent cohort.

Efficacy:

The log_{10} reduction in HCV concentrations (IU/mL) from pre-treatment to end on- or post-treatment was analysed by the mixed effects model. The proportion of patients with a viral load reduction by at least 2 log_{10} and the proportion of patients with an undetectable viral load were analysed by the Breslow-Day test.

Pharmacokinetics:

PK parameters were estimated using non-compartmental analysis. Dose-proportionality of PK parameters was assessed by an analysis of variance (ANOVA) or non-parametric techniques. Between genders comparisons used the same methods. BMI relationship with PK parameters was explored by correlation analysis. Drug-drug interaction was explored using confidence intervals (CIs).

Safety:

Treatment emergent adverse events (TEAEs) incidence was analysed by the Fisher's exact test. Safety lab parameters and ECGs were evaluated by an ANOVA for continuous variables and by the Fisher's exact test for categorical variables. Shift tables were produced for safety lab, vital signs, and ECGs.

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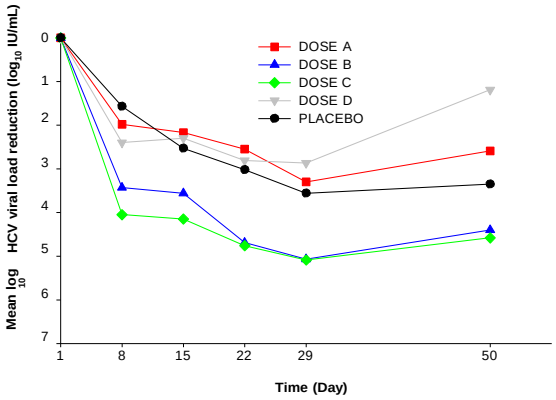
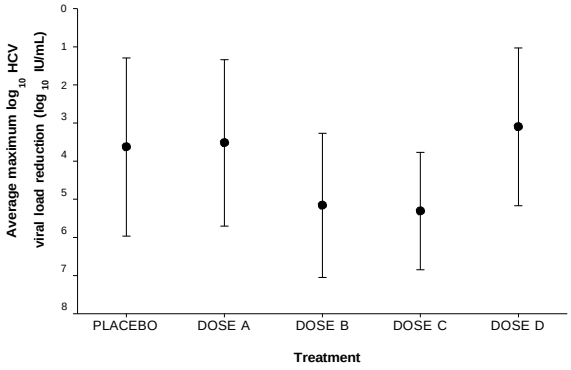
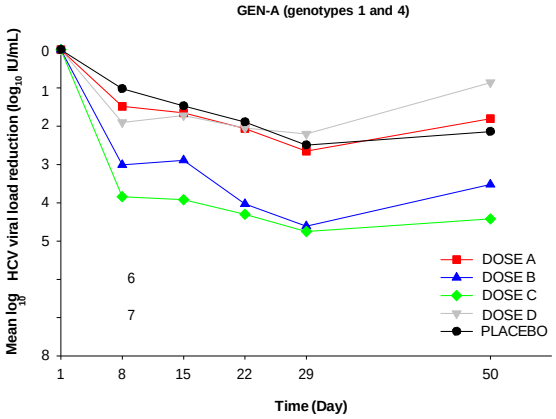
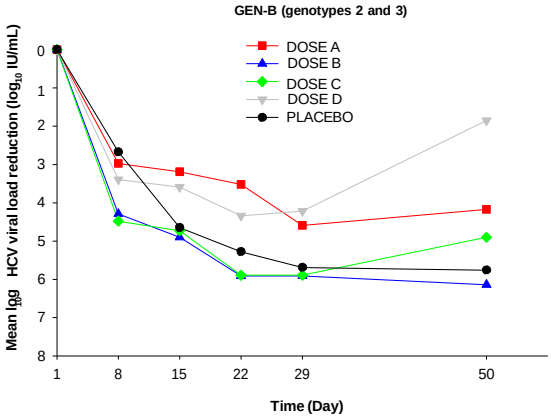
Summary of results:

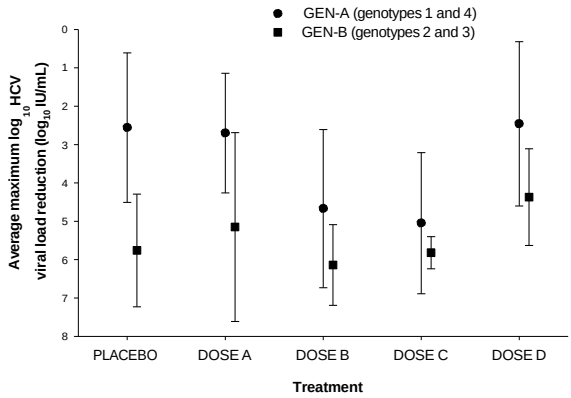
Efficacy:











Placebo (TX-4): PEGASYS®; **Dose A (TX-1)**: PEGASYS® + DEBIO-025 (200 mg); **Dose B (TX-2)**: PEGASYS® + DEBIO-025 (600 mg); **Dose C (TX-3)**: PEGASYS® + DEBIO-025 (1000 mg); **Dose D (TX-5)**: DEBIO-025 (1000 mg).

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	DEBIO-025 dose				
	(TX-4) Placebo + PEGASYS®	**(TX-1) 200 mg + PEGASYS®**	**(TX-2) 600 mg + PEGASYS®**	**(TX-3) 1000 mg + PEGASYS®**	**(TX-5) 1000 mg**
N	18	18	18	18	18
Viral load reduction (log_{10} IU/mL)					
Day 8	1.57 ± 1.21	1.98 ± 1.22	3.43 ± 1.19	4.05 ± 1.28	2.40 ± 1.62
Day 15	2.53 ± 2.19	2.17 ± 1.49	3.56 ± 1.52	4.15 ± 1.57 [a]	2.30 ± 1.98 [b]
Day 22	3.02 ± 2.25	2.55 ± 1.62	4.69 ± 1.81 [a]	4.76 ± 1.49 [a]	2.81 ± 2.18
Day 29	3.56 ± 2.37	3.30 ± 2.18	5.07 ± 1.73 [a]	5.09 ± 1.91 [a]	2.87 ± 2.28
Day 50	3.35 ± 2.44	2.59 ± 2.34	4.40 ± 2.70	4.58 ± 2.28	1.19 ± 1.71
Maximum viral load reduction (log_{10} IU/mL)	3.63 ± 2.34	3.52 ± 2.18	5.16 ± 1.89	5.31 ± 1.54	3.10 ± 2.07

Data form the ITT population

BLQ: < log (45 IU/mL) i.e. 1.65 IU/mL. [a] N = 17; [b] N = 16

Treatment with PEGASYS® and 1000 mg DEBIO-025 showed a more important decrease in viral load (TX-3; PE of the log_{10} difference: 1.28; 95% CI: 0.01 ; 2.54) than after administration of PEGASYS® alone, with a raw p-value of 0.048. The differences between this treatment and 1000 mg of DEBIO-025 alone (TX-5) was even larger (PE of the log_{10} difference: 2.02; 95% CI: 0.75 ; 3.28) with again a significant raw p-value of 0.002. These results indicate that 1000 mg DEBIO-025 is the minimal effective dose that induces an additive reduction in HCV viral load when combined with PEGASYS®. However, the maximum HCV viral load reduction after administration of PEGASYS® and 600 mg DEBIO-025 (TX-2; PE of the log_{10} difference: 1.24; 95% CI: 0.02 ; 2.51) was larger than after administration of PEGASYS® alone, with a raw p-value that showed a trend towards significance (p-value = 0.054). This suggests that a 600 mg dose of DEBIO-025 would probably also induce a significant additive effect in clinical studies with a larger sample size.

In general, a better response to all treatments was observed in the genotype 2 and 3 group (GEN-B) than in the genotype 1 and 4 group (GEN-A):

- in the GEN-A group, the viral load remained well above the LQ (1.65 log_{10} IU/mL) in treatment groups TX-1 (PEGASYS® and 200 mg DEBIO-025), TX-4 (PEGASYS® and placebo), and TX-5 (1000 mg DEBIO-025), while it was rapidly (by day 8) near or below the LQ with TX-3 (PEGASYS® and 1000 mg DEBIO-025) after start of administrations. Administration of TX-2 (PEGASYS® and 600 mg DEBIO-025) decreased viral load near the LQ by day 29. These data indicate an additive effect of the 600- and 1000-mg DEBIO-025 doses when combined with PEGASYS®. However the study was not powered to show a significant difference in the subgroups;
- in the GEN-B group, the viral load was rapidly (by day 8) decreased to a level close or below the LQ after treatment with TX-2, TX-3, and TX-5. Administration of TX-4 brought viral load near the LQ by day 15, while treatment TX-1 brought viral load near the LQ by day 29. Because of the already very important reduction of viral loads during treatment with PEGASYS® monotherapy, it was difficult to demonstrate any additive effect of DEBIO-025.

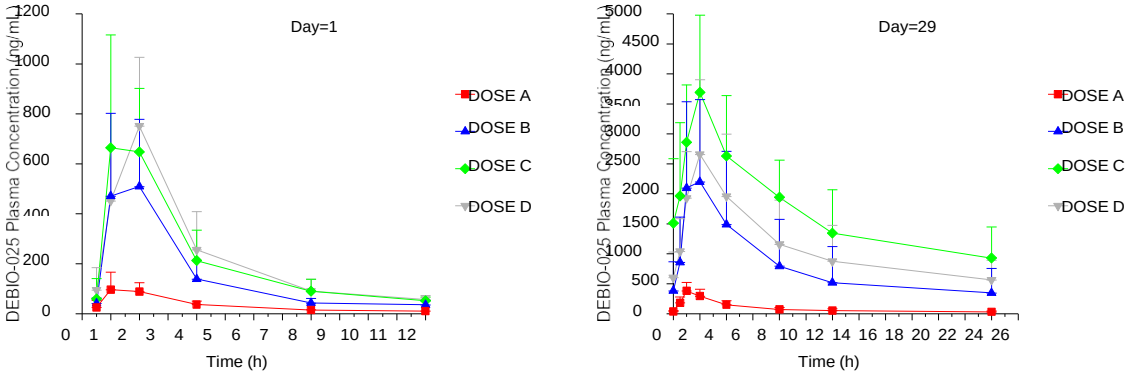
However, higher doses of DEBIO-025 seem to induce a faster drop of viral loads in the first weeks of treatment.

In spite of a better viral load reduction in the GEN-B group, no significant dose genotype class interactions were observed in both ITT and PP populations (p-values ≥ 0.32).

Pharmacokinetics:

DEBIO-025

The following DEBIO-025 profiles were obtained on days 1 and 29:



Dose A (TX-1): PEGASYS® + DEBIO-025 (200 mg); **Dose B (TX-2)**: PEGASYS® + DEBIO-025 (600 mg); **Dose C (TX-3)**: PEGASYS® + DEBIO-025 (1000 mg); **Dose D (TX-5)**: DEBIO-025 (1000 mg).

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DEBIO-025 PK parameters

	DEBIO-025 dose			
	(TX-1) 200 mg + PEGASYS®	(TX-2) 600 mg + PEGASYS®	(TX-3) 1000 mg + PEGASYS®	(TX-5) 1000 mg
N	16	11	10	10
Day 1				
C_{max} (ng/mL)	114 ± 65.5	606 ± 307	785 ± 381	775 ± 242
AUC_{0-12h} (µg.h/mL)	0.389 ± 0.140	1.88 ± 0.770[a]	2.36 ± 0.757[b]	2.70 ± 0.840[b]
t_{max} (h)	1.50 (1.00-2.00)	1.03 (1.00-2.00)	2.00 (1.00-2.05)	2.00 (1.00-4.00)
Day 29				
C_{max} (ng/mL)	404 ± 115	2290 ± 1380	3770 ± 1240	2710 ± 1200
AUC_{0-12h} (µg.h/mL)	1.61 ± 0.592	13.8 ± 11.4	27.0 ± 8.26	18.2 ± 10.3[c]
AUC_{0-24h} (µg.h/mL)	2.10 ± 0.817	18.9 ± 17.3	40.4 ± 14.4	26.5 ± 14.6
t_{max} (h)	1.00 (0.50-2.00)	1.00 (1.00-2.03)	2.00 (1.00-2.00)	2.00 (1.00-4.00)
AR_{AUC}	4.59 ± 2.17	6.35 ± 3.39[a]	12.7 ± 6.48[b]	6.79 ± 3.70[b]
AR_{Cmax}	4.65 ± 2.76	5.28 ± 6.63	6.08 ± 3.86	3.66 ± 1.40
$C_{ss\ av}$ (ng/mL)	87.5 ± 34.1	787 ± 721	1680 ± 599	1100 ± 606
C_{min} (ng/mL)	30.4 ± 17.1	308 ± 428	893 ± 527	537 ± 339
$Flux_i$ (%)	469 ± 162	329 ± 113	181 ± 77.8	231 ± 115
Cl/F (L/h)	113 ± 55.2	56.9 ± 39.6	26.8 ± 6.89	52.8 ± 40.7

Values are mean ± SD, except fot t_{max}: median (range). [a] n = 7; [b] n = 8; [c] n = 9

All patients had quantifiable DEBIO-025 concentrations by 30 min postdose. DEBIO-025 remained quantifiable in all postdose samples taken during the study, including the last samples (taken 21 days after the last administration) except in patients administered with 200 mg of DEBIO-025, for whom most of the values were BLQ. DEBIO-025 plasma exposure increased in general more than dose-proportionally, except on day 1 when exposure (both C_{max} and AUC_{0-12h}) was almost dose-proportional in the 600-1000 mg range and on day 29 when C_{max} was almost dose-proportional in the 600-1000 mg range. An accumulation of DEBIO-025 was observed from day 1 to day 29 with all treatments administered. Accumulation was in general 4 to 6 times the initial exposure except for TX-3, after which an almost 12-fold accumulation was observed.

A 40 to 50% higher DEBIO-025 plasma exposure was observed on day 29 in patients treated in combination with PEGASYS® as compared with those treated with DEBIO-025 alone, while exposure on day 1 was similar for both treatments. Despite a time-dependent effect of PEGASYS® could not be excluded, this difference could be related to a moderate to high inter-patients variability with respect to DEBIO-025 absorption and/or first pass effect.

In general, no significant gender effect was observed regarding PK parameters. No obvious relationship between DEBIO-025 PK parameters and the BMI could be derived.

No obvious differences between poor, intermediate, extensive, or ultrarapid metabolisers of cytochromes P450 2C9, 2C19, and 2D6, nor between different genotypes of ABCB1, were observed for the DEBIO-025 PK parameters.

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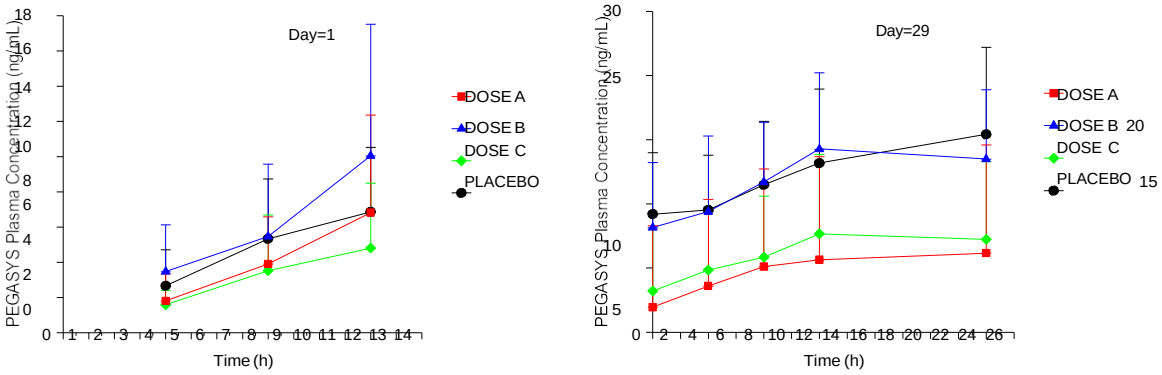
PEGASYS®

The following PEGASYS® profiles were obtained on days 1 and 29:



Dose A (TX-1): PEGASYS® + DEBIO-025 (200 mg); **Dose B (TX-2)**: PEGASYS® + DEBIO-025 (600 mg); **Dose C (TX-3)**: PEGASYS® + DEBIO-025 (1000 mg); **Placebo (TX-4)**: PEGASYS®.

PEGASYS® PK parameters:

	DEBIO-025 dose			
	(TX-4) Placebo + PEGASYS®	**(TX-1) 200 mg + PEGASYS®**	**(TX-2) 600 mg + PEGASYS®**	**(TX-3) 1000 mg + PEGASYS®**
N	9	16	11	10
Day 1				
C_{max} (ng/mL)	6.97 ± 3.68	7.00 ± 5.47	10.1 ± 7.39	4.81 ± 3.69
AUC_{0-12h} (µg.h/mL)	0.046 ± 0.028	0.036 ± 0.025	0.056 ± 0.039	0.030 ± 0.022
t_{max} (h)	11.9 (7.83-12.0)	12.0 (3.98-12.0)	11.9 (3.90-12.0)	11.9 (11.5-12.1)
Day 29				
C_{max} (ng/mL)	21.1 ± 6.11[a]	11.8 ± 8.83[b]	21.6 ± 5.28	13.7 ± 6.16[a]
AUC_{0-12h} (µg.h/mL)	0.181 ± 0.050[a]	0.109 ± 0.084[b]	0.184 ± 0.054	0.123 ± 0.055[a]
AUC_{0-24h} (µg.h/mL)	0.413 ± 0.121[a]	0.240 ± 0.181[b]	0.410 ± 0.110	0.272 ± 0.125[a]
t_{max} (h)	22.9 (0.00-24.0)[a]	23.8 (7.67-24.0)[f]	11.8 (0.00-23.9)	11.6 (0.00-24.0)[a]
AR_{AUC}	5.79 ± 3.31[a]	4.39 ± 3.97[b]	31.8 ± 90.0	7.82 ± 7.39[a]
AR_{Cmax}	3.96 ± 2.04[a]	2.79 ± 2.14[b]	8.75 ± 18.2	4.81 ± 3.33[a]
C_{min} (ng/mL)	12.9 ± 4.30[a]	6.91 ± 6.31[b]	11.3 ± 3.31	7.71 ± 4.51[a]

Values are mean ± SD, except for t_{max}: median (range); [a] n = 8; [b] n = 11; [f] n = 10

Most of the patients had quantifiable PEGASYS® concentrations by 4 h postdose. PEGASYS® remained quantifiable in most of the postdose samples taken during the study, including the last samples (taken 21 days after the last injection) except for TX-1.

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On day 1, PEGASYS® concentrations increased linearly over the first 12 h postdose, for all treatments. On day 29 predose, there was a difference of concentration between patients administered with TX-1 and TX-3 who had lower concentrations than those administered with TX-2 and TX-4. After administration of PEGASYS® an increase of concentration was observed during 12 h and then remained roughly steady over the next 12 h for all treatments. An accumulation (2 to 6 times) of PEGASYS® was observed from day 1 to day 29 with all treatments administered.

While PEGASYS® plasma exposure was almost similar on day 1 for all treatments, a lower exposure was observed on day 29 in patients treated in combination with DEBIO-025 as compared with those treated with PEGASYS® alone. However, this was not correlated with the DEBIO-025 dose: lower exposure by an estimated 60-70% for TX-1 (200 mg), 10% for TX-2 (600 mg), and 50% for TX-3 (1000 mg). In addition, this was in general not statistically significant (except for TX-1) and the inter-individual variability was very high. Altogether, despite it could not be formally excluded, this indicated that an interaction of DEBIO-025 towards PEGASYS® PK was unlikely.

No significant gender effect was observed regarding PK parameters (p-values $\geq$ 0.188). No obvious relationship between PEGASYS® PK parameters and the BMI could be derived.

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Safety:

As summarised in the table below, 87 patients (97%) experienced at least 1 TEAE during the treatment period.

	DEBIO-025 dose					
Event	(TX-4) Placebo + PEGASYS® (N=18)	(TX-1) 200 mg + PEGASYS® (N=18)	(TX-2) 600 mg + PEGASYS® (N=18)	(TX-3) 1000 mg + PEGASYS® (N=18)	(TX-5) 1000 mg (N=18)	All patients (N=90)
TEAE	152	109	125	137	87	610
	18 (100)	16 (89)	18 (100)	17 (94)	18 (100)	87 (97)
TEAE in ≥ 20% of patients						
Headache	23	21	25	15	8	92
	12 (67)	12 (67)	11 (61)	10 (56)	8 (44)	53 (59)
Pyrexia	18	11	15	6	-	50
	13 (72)	6 (33)	10 (56)	6 (33)		35 (39)
Nausea	12	2	3	10	9	36
	8 (44)	2 (11)	3 (17)	7 (39)	8 (44)	28 (31)
Myalgia	12	7	7	7	1	34
	8 (44)	4 (22)	4 (22)	5 (28)	1 (6)	22 (24)
Fatigue	7	1	2	10	7	27
	6 (33)	1 (6)	2 (11)	9 (50)	7 (39)	25 (28)
Chills	8	7	5	3	-	23
	6 (33)	5 (28)	4 (22)	3 (17)		18 (20)
Severe TEAE	13	2	5	12	6	38
	4 (22)	1 (6)	2 (11)	5 (28)	3 (17)	15 (17)
Treatment-related TEAE	40	24	25	43	64	196
	11 (61)	6 (33)	7 (39)	12 (67)	13 (72)	49 (54)
Treatment-related TEAE in ≥ 10% of patients						
Headache	7	5	6	5	6	29
	7 (39)	3 (19)	4 (22)	4 (22)	6 (33)	24 (27)
Nausea	9	2	2	6	8	27
	5 (28)	2 (13)	2 (11)	4 (22)	7 (39)	20 (23)
Hyperbilirubinaen ia	-	-	-	5	8	13
				5 (28)	8 (44)	13 (15)
Fatigue	2	-	-	1	6	9
	2 (11)			1 (6)	6 (33)	9 (10)
TEAE leading to discontinuation	-	-	1	2	1	4
			1 (6)	2 (11)	1 (6)	4 (4)

Values are number of events; number of patients with event (percentage within the group)

TEAEs were the most frequent in the placebo group (152) and the least frequent in the group with no PEGASYS treatment (87); 109 to 137 TEAEs occurred in the 3 groups treated with DEBIO-025 + PEGASYS®. The most frequent TEAEs included flu-like symptoms (headache, pyrexia, myalgia, and chills), which were related to PEGASYS administration since they were much less frequent in the TX-5 group and were consistent with the expected side effects of PEGASYS®. Hyperbilirubinaemia

was observed in 13 patients treated with 1000 mg DEBIO-025 and pruritus was much more frequent in patients treated with DEBIO-025 600 mg or higher (9 patients vs. 1 placebo patient).
Thirty-eight (38) severe TEAEs occurred in 15 patients (17%) during the treatment period. Distribution of severe events in the treatment groups was similar to the distribution of all TEAEs. The most frequent severe AEs were flu-like symptoms.

In 49 patients, 196 TEAEs (54%) were considered to have a reasonable causal relationship with study drug during the treatment period. The most frequent treatment-related AEs included headache, nausea, hyperbilirubinaemia, and fatigue. Treatment-related hyperbilirubinaemia and pruritus occurred only in the 2 groups treated with 1000 mg DEBIO-025 (hyperbilirubinaemia: in 5 patients or 28% of the TX-3 group and 8 patients or 44% of the TX-5 group; pruritus: in 3 patients or 17% of the TX-3 group and 2 patients or 11% of the TX-5 group).

In 16 patients, 23 AEs occurred (18%) during the follow-up phase. Only one was considered as treatment-related (one case of mild pain in extremity).

No serious AEs (SAEs) occurred during the study. Four patients discontinued the study because of an AE: 1 patient with moderate abscess (TX-2), 1 patient with mild abnormal feeling, moderate nausea, and moderate pain (TX-3), 1 patient with moderate hypertension (TX 3), and 1 patient with hyperbilirubinaemia (TX-5). The patients recovered from all these AEs before the end of the study. One patient temporarily interrupted the TX-3 treatment following allergic dermatitis, hyperbilirubinaemia, and pruritus.

Sixty-two (62) TEAEs were not resolved by the end of the study.

All cases of hyperbilirubinaemia were observed in the patients treated with 1000 mg DEBIO-025 and were all considered to have a reasonable causal relationship with the study medication as hyperbilirubinaemia is a common side effect of the DEBIO-025 treatment. The hyperbilirubinaemia is caused by the inhibition of the the biliary canalicular transporter MRP2, which results in an increase in conjugated bilirubin. The present data confirm the results from the previous study: the effect is dose dependent and fully reversible after treatment cessation. Also in this study, none of the patients with increased bilirubin had associated increases of transaminases, alkaline phosphatases or gamma-glutamyltransferase (GGT), indicating that this is a pure cholestatic phenomenon. Hyperbilirubinaemia is the most important dose-limiting factor for the administration of DEBIO-025 identified so far.

At the highest dose of 1000 mg, DEBIO-025 induced an additive reduction in thrombocytes when combined with PEGASYS® and this will require careful monitoring of platelet functions in further studies.

Clear changes in bonemarkers and cholesterol were observed that did not induce any clinical symptoms and were reversible after treatment. Whether these changes will become clinically relevant during prolonged treatment will depend on the duration of the future treatment with DEBIO-025. Therefore, careful evaluation of bone and lipid metabolism needs to be planned in phase II and III studies.

The importance of the other lab changes (LDH, urea and fibrinogen) is unclear, and will need further evaluation in long-term studies.

Name of sponsor: Debiopharm International S.A.	**Individual study table referring to module 5 of the dossier**	**(For national authority use only)**
Name of finished product: NA	**Volume:**	
Name of active ingredient: DEBIO-025	**Page:**	

Conclusions:

The Minimal Effective Dose of DEBIO-025 that generated an additive reduction in viral load in combination with PEGASYS® was defined as 1000 mg. However, the 600-mg dose had also an additive effect, but this did not reach statistical significance because of the small sample size of this exploratory study. The additive antiviral effect was more evident in the patients with genotype 1 and 4 than in the group with genotype 2 and 3, because of the already near-maximal antiviral effect in the latter group.

Following administration for 29 days at doses of 200 to 1000 mg o.d. (b.i.d. during the first week), DEBIO-025 plasma exposure increased in general more than dose-proportionally and showed an important accumulation. No clear relationship between the DEBIO-025 concentrations and the HCV viral load reduction could be observed.

On the last day of treatment, a ca. 50% higher DEBIO-025 plasma exposure was observed in patients treated in combination with PEGASYS® as compared with those treated with DEBIO-025 alone. Despite a time-dependent effect of PEGASYS® could not be excluded, this difference could be related to a moderate to high inter-patient variability with respect to DEBIO-025 absorption and/or first pass effect.

On the last day of the administration period at a dose of 180 µg weekly, a lower PEGASYS® plasma exposure was observed in patients treated in combination with DEBIO-025 as compared with those treated with PEGASYS® alone, by an estimated 60-70% with 200 mg of DEBIO-025, 10% with 600 mg of DEBIO-025, and 50% with 1000 mg of DEBIO-025. However, this was not correlated with the DEBIO-025 dose and inter-individual variability was very high. Altogether, despite it could not be formally excluded, this indicated that an interaction of DEBIO-025 towards PEGASYS® PK was unlikely.

Administration of 200 mg or 600 mg DEBIO-025 combined with 180 µg PEGASYS® seemed well tolerated (the majority of reported AEs were known side effects of PEGASYS®, especially flu-like symptoms). Isolated hyperbilirubinaemia was a dose-limiting AE, which occurred only during treatment with 1000 mg DEBIO-025. Other AEs that may have an influence on the long term dosing regimen of DEBIO-025, which will require specific monitoring in future studies, are reduction of thrombocytes and increases in cholesterol and bone markers.

In conclusion, 600 mg DEBIO-025 in combination with 180 µg PEGASYS® seems to be the treatment that shows the best balance between additive antiviral effect on HCV and safety.

GCP Statement: This study was performed in compliance with the current version of the declaration of Helsinki and with the ICH note for guidance on good clinical practice (CPMP/ICH/135/95), including the archiving of essential documents.

Amendments: There were two amendments to the protocol:

- amendment 1 was issued on 14-Nov-2006 to clarify the protocol (correction of inconsistencies and typographical errors, clarification of figures, widening of a few normal ranges, etc.) and to add an additional laboratory test (HCV strain sequencing);
- amendment 2 was issued on 18-Dec-2006 to add an additional blood sampling on day 1, 29, and 50.

Date of the report: 04-Mar-2008 (Final)